

Transposition of great arteries

A study of 65 infants followed for 1 to 4 years after balloon septostomy

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Though the outlook for children with transposition of the great arteries has been transformed by modern methods of treatment, the initial improvement after balloon septostomy may raise false hopes. A relatively long follow-up of the first 65 consecutive cases treated between November 1966 and December 1969 shows the serious risks to which these infants are exposed: 32 children have died, 5 during or immediately after septostomy; 18 needed further septostomies and 12 of these have died. The influence of coexistent heart lesions has been analysed and the effect on pulmonary vascular resistance assessed, demonstrating that a ventricular septal defect or a persistent ductus arteriosus does not always need surgical treatment to prevent pulmonary hypertension. Intravascular thrombosis was a major problem causing serious damage to brain, kidneys, and intestine, and 9 deaths. Mustard's operation produced immediate improvement but the long-term prognosis has still to be assessed.

Balloon atrial septostomy (Rashkind and Miller, 1966) and subsequent surgical correction (Mustard, 1964) have revolutionized the management of infants with transposition of the great arteries. In this paper we review the first 65 infants with transposition to be treated by balloon septostomy at Birmingham Children's Hospital. The babies were admitted between November 1966 and December 1969; cases of tricuspid atresia have been excluded.

Balloon septostomy is quick, it causes little disturbance, and usually gives satisfactory immediate results. When successful there is an obvious improvement in the child's colour, a rise in oxygen saturation in right atrial blood, abolition of pressure gradient between the two atria, and a hole large enough to pass the inflated balloon in either direction without difficulty. But initial improvement is not always maintained, and a review of patients followed up for 1 to 4 years or more shows the hazards to which these children are exposed especially in the interval between septostomy and Mustard's operation.

Results

Repeat septostomy A second septostomy (Table 1) was needed on 18 occasions – by balloon in 13 and operation in 5. Six of the

infants treated twice by balloon required a third (surgical) septostomy and this has led to the conclusion that the Blalock-Hanlon (1950) procedure should be used when a second septostomy is necessary. In some cases the surgeons found a tough septum and little evidence of a previous tear, suggesting that the balloon had merely stretched the foramen ovale, though with considerable improvement perhaps for several weeks. There is no evidence that this was anything to do with age; it happened as often in newborn babies as in older children.

Deaths Of the 65 infants, 32 have died (Table 2). Of 5 'immediate' deaths, 4 oc-

TABLE 1 *Age at initial septostomy related to need for additional septostomy*

Age group	Initial septostomy (all balloon)		Repeat septostomy (some surgical)		Total deaths	
	Infants	Immediate deaths	Second	Third	Later deaths	All causes
0-7 dy	28	1	8	3	4	13
8-28 dy	25	2	8	2	6	12
1 mth or over	12	2	2	1	2	7
	65	5	18	6	12	32

TABLE 2 Probable cause of 32 deaths after initial septostomy in 65 cases

Immediate	Cardiac arrest	4
	Perforated atrium	1
Intermediate	Thrombosis	9
	Heart failure	7
	Pneumonia	4
	Blalock-Hanlon	2
	Unknown	3
Late	Corrective surgery	2
Total		32

curred during septostomy, perhaps because the procedure was too long delayed or because in 1967 the urgent need to correct metabolic acidosis had not been fully appreciated. Certainly at that time cardiac arrhythmias were commonly observed during septostomy and included ectopic beats, paroxysmal tachycardia, atrial flutter and fibrillation, partial and complete atrioventricular block, ventricular tachycardia, fibrillation, and standstill. The fifth death in this group was a baby whose left atrium had been perforated by the catheter. Though there was no tamponade, he survived for only a few hours and at necropsy was shown to have aortic coarctation, severe pulmonary stenosis, and a ventricular septal defect in addition to transposition of the great arteries.

There were 25 deaths in the intermediate period – months or years after initial septostomy but before Mustard's operation could be done. Nine resulted directly from thrombosis. Seven were ascribed to heart failure and of these 2 had had pulmonary artery banding to control pulmonary hypertension, 4 probably had inadequate relief from septostomy, and 1 had a single ventricle and hypoplastic pulmonary artery. Two babies succumbed during or shortly after surgical atrial septostomy, and 3 deaths were unexpected and unexplained, 2 children dying suddenly at home after progressing well for nearly a year, and a 2-year-old who collapsed and died shortly after being admitted to hospital for Mustard's operation. Attempts at resuscitation failed; necropsy revealed a satisfactory interatrial communication, transposition of the great arteries, and no other defect or explanation of the cardiac arrest.

Two patients died shortly after Mustard's operation.

Coexistent heart defects As a prelude to balloon septostomy angiocardiology was

used to confirm the diagnosis, and other defects complicating transposition could usually be shown by this method. Cardiac catheterization was at first deferred until shortly before corrective operation, but we now investigate the child fully at about 6 months because we have found it difficult to recognize pulmonary hypertension and complicating defects by clinical examination, radiography, or electrocardiogram. The results of haemodynamic studies in this group of children will be included in a larger study which is to be published shortly.

Until we obtained a Muller ASIC catheter (Grollman *et al.*, 1968) the pulmonary artery was seldom entered. In such cases, if left ventricular pressure was high and pulmonary stenosis had been excluded by angiocardiology, a lung biopsy was sometimes examined. In fact we failed to diagnose pulmonary stenosis on two occasions, but when recognized as a cause of unsatisfactory progress it was treated by creating an anastomosis between either aorta or superior vena cava and pulmonary artery.

An operation is usually advised to prevent pulmonary hypertensive changes when a ventricular septal defect or persistent ductus arteriosus complicates transposition of the great arteries (Shaher and Kidd, 1968; Stark *et al.*, 1970). Table 3 summarizes what happened to the ventricular septal defect in the 19 cases diagnosed at initial angiocardiology and re-examined at necropsy or at cardiac catheterization before operation. Of these 19 children, 11 also had a persistent ductus arteriosus; 4 had a ductus alone. A high proportion closed spontaneously and these had a normal pulmonary vascular structure when

TABLE 3 Course of disease in transposition of great arteries complicated by ventricular septal defect or persistent ductus arteriosus (deaths in parentheses)

Outcome	Ventricular septal defect	Persistent ductus arteriosus
Spontaneous closure	5 (4)	5 (5)
Open		
Died at septostomy	3 (3)	3 (3)
Normal pulmonary artery pressure	4	3 (1)
Pulmonary stenosis	2	1
Raised pulmonary artery pressure		
Normal biopsy	1 (1)	—
Inoperable	1	—
Pulmonary artery banded	3 (2)	—
Persistent ductus arteriosus ligated	—	2 (2)
Aortic arch hypoplasia	—	1 (1)
Total	19 (10)	15 (12)

examined at necropsy. Some died before operation could be contemplated. We were certainly guilty of failing to recognize pulmonary stenosis in 2 cases (which were treated surgically elsewhere) and pulmonary hypertension in one case. Two children had pulmonary artery banding in other hospitals.

Other heart defects found in this group of 65 children include pulmonary stenosis (4), double outlet right ventricle (1), hypoplastic left heart syndrome (3), and dextrocardia (1). Some children had more than one abnormality. Aortic coarctation and transposition of the great arteries were noted in 4 patients, all of whom died: 2 of these were infants treated early in the series; inadequate communication between the atria was almost certainly responsible; a third baby died during septostomy and when examined at necropsy was found to have subdural and subarachnoid haemorrhages; the fourth boy was well for 2½ years, and then, 10 days after resection of the coarctation as a preliminary to Mustard's operation, he had occlusion of a femoral vein, femoral artery, renal vessels, middle cerebral artery, and cerebral venous sinuses; there was no clot on the aortic suture line.

Effects of vascular obstruction

Intravascular clotting has proved a major problem (Table 4) with consequences that were sometimes negligible but sometimes catastrophic. On other occasions symptoms were temporarily severe but abated quickly and completely, suggesting incomplete and transient vascular blockage.

Cerebral vascular disturbances These had a characteristically slow onset followed by one of two different syndromes, the hemiplegic and the hydrocephalic. In 7 cases restlessness, screaming attacks, irritability, loss of appetite, vomiting, fits, or weakness of a limb were followed after several days by hemiparesis. Seven children developed the hydrocephalic syndrome. Characteristically a haunting look of terror was the prelude to sudden deterioration when irritability gave way to

lethargy and coma. Deep sighing respiration of Kussmaul type was not relieved by correcting metabolic acidosis. Signs of increasing intracranial pressure, with a tense bulging anterior fontanelle and congested scalp and intraocular veins, were followed by papilloedema, periorbital oedema, and sometimes squints. The cerebrospinal fluid protein level was raised to about 100 mg/100 ml. Attacks were occasionally repeated; 2 children had both types of syndrome.

The 9 children who died were found to have a dilated cerebral ventricular system with extensive infarction and softening of the brain. Venous sinus thrombosis was usual, but arterial thrombosis was also seen and 2 children had occlusion of internal carotid arteries only. A survivor had arrested hydrocephalus. During the acute episode at the age of 6 months his skull circumference increased from the 3rd to the 90th centile over a period of 10 weeks. His head has remained large; he did not talk until he was 3 or walk until he was 4, but in other respects recovery has been good. The rate of improvement increased after Mustard's operation. All surviving children show slight mental impairment.

FIG. 1 Straight x-ray of abdomen of infant with mesenteric artery thrombosis. Fluid levels in small bowel and gas in colon.

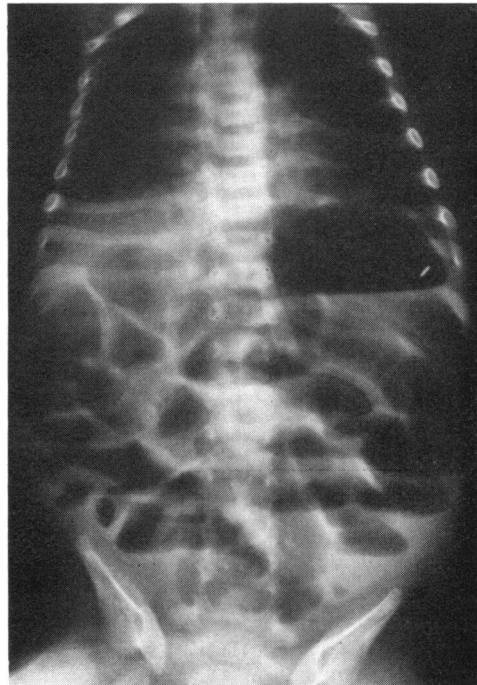


TABLE 4 Site of thrombosis excluding those affecting veins in limbs

Organs affected	Proved	Suspected
Brain hemiplegia	7	—
'Hydrocephalus'	7	2
Kidney	1	2
Gut (mesenteric vessels)	2	5
Leg (femoral artery)	1	—

Disturbances of intestinal activity These were common and on occasion recurrent diarrhoea has been sufficiently severe for the child to be investigated for infection, carbohydrate intolerance, mucoviscidosis, and malabsorption. Possibly these upsets were due to a sluggish mesenteric circulation. Alternatively diarrhoea may have caused dehydration which resulted in mesenteric thrombosis.

When encountered, this condition too was remarkable for the leisurely march of symptoms. A fickle appetite, colic, and grumbling diarrhoea with blood in the stools were followed by infrequent and then by more persistent vomiting. The abdomen became distended and bowel sounds almost – but never quite – ceased. Radiography showed fluid levels in the small bowel but gas in the colon (Fig. 1). Indeed the most characteristic feature was the lack of conclusive evidence of complete obstruction. Laparotomy was carried out twice but only after prolonged debate, and even at operation the findings were inconclusive. The gut was distended and congested but not necrotic and in neither child was bowel resected. In both, however, deterioration and death followed within a few days and thrombosis of the superior mesenteric artery was clearly seen in the case which came to necropsy.

The diagnosis was suspected but not proved in 5 other children. The typically slow onset with colic and blood in the stools was followed by vomiting and a distended almost silent abdomen. Four of the group died but permission for necropsy was refused. The fifth child recovered. Each of the 5 had had cerebral vascular accidents, one developed signs of inferior vena cava thrombosis shortly before dying, and one had had obvious haematuria. There is therefore no doubt about their liability to thrombosis.

Urinary disturbances When there was frank haematuria or urinary suppression at the same time as other clearly recognizable thrombotic symptoms, we thought it reasonable to assume that there had been renal infarction. This diagnosis was suspected but not proved in 3 children; it has been proved at necropsy in patients who are not included in this group of 65 infants.

Cause of vascular obstruction

No one who has attempted to aspirate blood from a deeply cyanosed baby with transposition of the great arteries will doubt that blood viscosity is high. The blood is tarry and the circulation sluggish. Venesection and haemo-

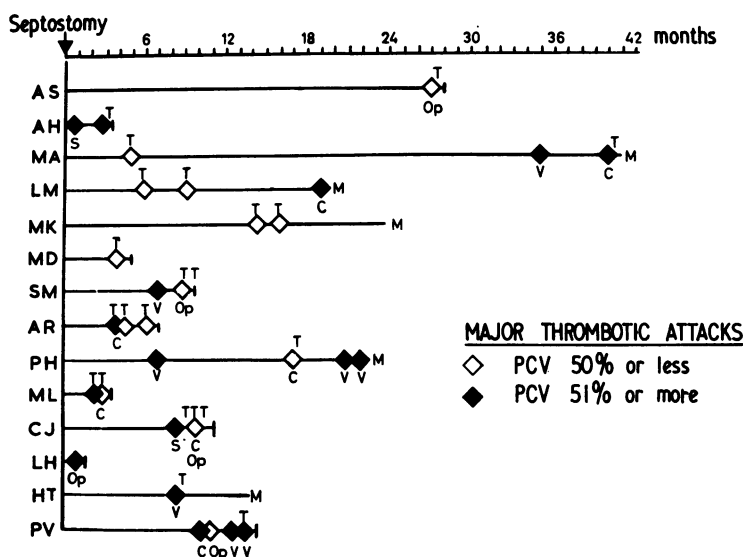


FIG. 2 Bar chart summarizing history of children who had thrombotic episodes. T, thrombosis; M, Mustard's operation; Op, other operation; S, septostomy; V, venesection; C, cardiac catheterization; I at end of bar indicates death.

dilution have a dramatic effect, transforming dullness and apathy into alertness and liveliness.

Intravascular clotting was usually preceded by a story suggestive of slowly progressive vascular obstruction. However, we failed to prevent complete occlusion by giving heparin, phenindione, or warfarin during the premonitory period which sometimes lasted a week. Using a cardiac catheter or performing a surgical operation has precipitated thrombosis within a matter of hours (Fig. 2). In fact clotting has followed directly after venesection and haemodilution undertaken because symptoms suggested that thrombosis was threatening. Somewhat surprisingly, thrombosis occurred almost as frequently when the packed cell volume was 50 per cent or less as when it was abnormally high.

From Fig. 2 it can be seen that a patient may have repeated thromboses, not always affecting the same organ, and that the interval between attacks can vary from a few days to 3 years. The longest interval was in the boy already mentioned, with the hydrocephalic syndrome. A temporary recurrence of symptoms – coma, air hunger, papilloedema, and periorbital oedema – followed an hour or so after cardiac catheterization done at the age of 3½ years as a preliminary to corrective opera-

tion. No further trouble has been encountered since Mustard's operation.

The risk of clotting was greatest between 4 months and 18 months of age and the youngest infant to be affected was 2½ months old. (We have since seen cerebral venous thrombosis with hemiparesis in a baby aged 6 weeks. This was followed by intestinal obstruction and urinary suppression. Necropsy showed organized clot on the atrial wall near the septostomy tear and large clots in the descending aorta and at the aortic bifurcation. The packed cell volume did not exceed 54 per cent while the child was in hospital.)

Discussion

An extremely well-documented analysis of the natural history of transposition of the great arteries by Liebman, Cullum, and Belloc (1969) provides a timely reminder of the appalling prognosis when no treatment is given. In a previous paper (Singh, Astley, and Burrows, 1969) we commented on the satisfactory immediate response to balloon septostomy. We remain satisfied that this is the initial treatment of choice but analysis of the history of a consecutive series of 65 patients followed up for a relatively long time shows a disappointingly high mortality and morbidity during the wait for corrective operation. Our experience is not unique for, in a 2½-year follow-up of 31 cases, Rashkind and Miller (1968) mention 5 early and 4 late deaths, 2 infants with strokes, and 3 who needed a second septostomy. Likewise, Venables (1970) describes his experiences with 26 infants seen in a little less than 3 years. At the end of his study only 9 children survived; 3 early deaths were ascribed to inadequate mixing of blood through the atrial septal defect and 4 to atrial perforation. Four children of the 11 observed for more than 6 months needed a second septostomy. At least one child had a cerebral venous thrombosis.

Most of the immediate deaths in our series were due to arrhythmias and all happened in 1966–67, early in our experience of the method. In the Co-operative study on cardiac catheterization organized by the American Heart Association the danger of catheterization in small infants was pointed out by Braunwald (1968) and by Braunwald and Gorlin (1968). They commented on the high mortality – 6 per cent – during the first 2 months when risks of perforation, arrhythmia, and deterioration during the procedure were at their highest. Infants with transposition of the great arteries were especially vulnerable. In an analysis of the underlying reasons for these high risks, Rudolph (1968) drew attention to

the dangers resulting from metabolic acidosis, cooling, oversedation, and failure to administer oxygen in sufficient concentration. Most babies with transposition are severely acidotic before the balloon catheter is introduced, and there is no doubt that urgent attention to these details of management reduces the risks from cardiac arrhythmias.

The initial balloon septostomy is a hazard in itself, for catheterization alone carries a mortality of up to 12 per cent in infants with transposition (Krovetz, Shanklin, and Schiebeler, 1968). There are the additional risks of being unable to deflate the balloon (Ellison *et al.*, 1970; Scott, 1970), and there can be no guarantee that the hole torn in the septum will be sufficiently large, as is the case when a surgeon is responsible.

It may be difficult to decide when to band the pulmonary artery of an infant with a complicating ventricular septal defect or to operate on a persistent ductus arteriosus. Our practice now is to undertake full catheter studies for babies who have continuing heart failure, and anyway at the age of 6 months, and to operate on those who have pulmonary hypertension. We have shown that both ventricular septal defect and persistent ductus arteriosus may close spontaneously and that, even when this does not happen, pulmonary hypertension is not an inevitable sequel.

Cyanotic congenital heart disease upsets the clotting mechanism (Ekert *et al.*, 1970; Komp and Sparrow, 1970; Naiman, 1970). Like Gross, Keefer, and Liebman (1968), we have found that older children are likely to bleed whereas those under the age of 3 have a tendency to clot. We have shown that thrombosis in transposition of the great arteries may occur with a packed cell volume of 50 per cent or less, and Gross and his colleagues also noted that cyanotic children might suffer from thrombosis before polycythaemia had time to develop.

Polycythaemia and increased viscosity go hand in hand (Kontras *et al.*, 1970), and a severely cyanosed child responds to phlebotomy by becoming much brighter and more active. This led us to bleed our patients when the haematocrit reading was 60 per cent or more, but we have been increasingly disturbed by the association between phlebotomy and the onset of thrombosis. We noticed on a number of occasions that slowly progressive deterioration was followed immediately after catheterization or venesection by a sudden worsening of the child's condition, and that the thrombosis which appeared to be responsible was not necessarily limited to the intubated vein. A recent review of intra-

venous catheterization in a neonatal unit (Wigger, Bransilver, and Blanc, 1970) revealed that 12.5 per cent of the infants had a major thrombosis as a consequence. In 75 per cent of the affected infants major organs were involved – lungs, brain, kidneys, or limbs – and thrombosis was the eventual cause of death in 12 per cent. They suggest that thrombosis resulted from the catheter damaging the intima, followed by release of adenosine diphosphate and platelet aggregation. Stark *et al.* (1970) mention a patient with transposition of the great arteries who died of multiple venous and arterial thromboses shortly after banding of the pulmonary artery; pressures had been measured in the heart and vessels during operation.

Apart from the risk of precipitating thrombosis, the relief afforded by bleeding is only temporary and consequently there seems little justification for the method. We have used oral anticoagulants in an attempt to prevent clotting but have insufficient experience to assess their value. Certainly it can be difficult to regulate the dose of warfarin or phenindione in a small baby. In fact the only effective way to deal with polycythaemia is to improve tissue oxygenation. Persistent cyanosis and a high packed cell volume are indications for operation. For infants this means ensuring adequate interatrial communication and perhaps dealing with coexisting heart defects (Plauth *et al.*, 1968). Larger children need corrective surgery (Mustard, 1964; Mustard *et al.*, 1964; Aberdeen *et al.*, 1965).

Mustard's operation has a low mortality and quickly relieves symptoms. Fourteen children have been treated in this series with 2 deaths. Thrombosis has not been seen after operation. The long-term results have yet to be determined, but, since the expected life span of a patient with naturally occurring corrected transposition is reduced, it is likely that this will happen after this kind of surgical correction. Apart from the possibility of right ventricular failure the risks seem to be of arrhythmias and of pulmonary hypertension. Arrhythmias have been common during septostomy. Paroxysmal tachycardia has not been observed in the interval between septostomy and Mustard's operation, but after operation attacks have been very troublesome and difficult to control in two patients. Transient atrioventricular block was seen during operation but there has been no example of persistent complete block. It is probable that the 3 children who died unexpectedly may have had some form of cardiac arrhythmia. The child who died in hospital certainly had a cardiac arrest, and it may be significant that

he had a high pulmonary artery pressure (39/27 mmHg) but a normal lung biopsy.

Pulmonary artery pressure was checked by cardiac catheterization before patients were accepted for operation. All cases chosen, including 12 who still await surgery, had a normal pulmonary artery pressure. Only time will show whether progressive changes develop in the pulmonary vessels, especially in these children who had a complicating ventricular septal defect or a persistent ductus arteriosus. Viles, Ongley, and Titus (1969) showed abnormalities in the pulmonary vasculature in transposition of the great arteries even when there was coexistent pulmonary stenosis. We have not felt it justifiable to repeat our haemodynamic studies after Mustard's operation because it is difficult to see how this could benefit children with a rising pulmonary vascular resistance, but it is our impression that this may be happening in one or two cases.

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